

Improvement of the T.R.U.E. Test: Launch of Panel 3

To the Editor:

By the early 1960s, patch testing had come into its own, and independently running clinics were widespread throughout Europe and the Americas. In 1962 the Scandinavian Committee for Standardization of Routine Patch Testing set forth to unify the European clinics by formalizing the patch-testing procedure. By the late 1960s, this same process was under way in the Americas, with the North American Contact Dermatitis Group (NACDG) at the helm.¹ Despite this, approximately two decades later, the Food and Drug Administration (FDA) proposed a ban on the production and sale of allergens for the patch tests, purportedly based on the lack of availability of scientific evidence for the safety and efficacy of the procedure.¹

During the 1980s, Pharmacia pioneered the development of bioavailable allergen preparations as thin flexible homogenous gels that readily rehydrated with skin contact. And finally, in 1994, through the cooperative efforts of scientists, academicians, and industry, the "24-allergen" Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) Test gained FDA approval for sale in the United States.²⁻⁴

The development of the T.R.U.E. Test panels 1.1 and 2.1 was a significant accomplishment, requiring the identification of highly relevant allergens and appropriate concentrations as well as analytical methods development, process engineering, and stability testing. Dose-response trials, bioequivalence trials, and extensive safety and efficacy studies were performed in patch-test clinics around the world.⁴ This resulted in a clinically effective first-line screening tool, with a validated manufacturing process. The clinical utility was evidenced by the fact that approximately 62% of 3,120 patients (NACDG 1994–1996 data) had at least one positive reaction to an allergen present on the T.R.U.E. Test panels 1.1 and 2.1.⁵

Despite its ease of use, the T.R.U.E. Test has frustrated

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Figure 1. New T.R.U.E. Test panel 3. (Reproduced with permission from Allerderm Clinical Research Department, Phoenix, AZ, and Mekos Laboratories, Hillerød, Denmark.)

US dermatologists owing to the seemingly glacial pace of adding new allergens.⁴ The lengthy development time is the result of standardized clinical trials and manufacturing process validation required for US licensure. T.R.U.E. Test is an FDA-registered biologic, with testing and manufacturing controls similar to those of skin-prick allergens (pollens, cat dander, etc) and vaccines. Even small changes in formulations, excipients, allergens, and tape composition can necessitate the full range of clinical testing, process validation, and stability studies. As a result, each allergen requires, at a bare minimum, 3 to 5 years of development and several hundred thousands in research dollars.

By 2001, several new and important T.R.U.E. Test allergens were in development or clinical trials, including tixocortol-21-pivalate, budesonide, imidazolidinylurea (Germall 115, ISP Sutton Laboratories, Chatham, NJ), diazolidinylurea (Germall II), and an improved and reformulated quinoline mix.⁴ Selected on the basis of observations of dermatologists in the NACDG, the European Environmental and Contact Dermatitis Research Group, and the European Society of Contact Dermatitis, as well as published prevalence data, these allergens were submitted to the FDA between 2004 and 2005. Now nearing final FDA approval and release, these allergens will form US panel 3.1 (which will be slightly different than the European panel)^{5,6} (Allerderm Clinical Research Department, Phoenix, AZ, and Mekos

Laboratories, Hillerød, Denmark, personal communication, July 2007) (Fig 1).

In addition to the five allergens described above, clinical trials of the remaining seven allergens for panel 3 are also under way. Their selection was again based on input from the NACDG and European contact dermatitis groups (Table 1). These allergens and the completed panel are anticipated for FDA submission in late 2008, resulting in a global increase in the ability to detect clinically relevant allergens.

Of course, not all allergens are suitable for T.R.U.E. Test development, owing to limitations in the formulation or production processes. For example, the allergenic uncured methymethacrylate monomer is volatile, unstable, and possibly unsafe for workers to handle during manufacture. Owing to these types of practical limitations and the time required for development, it is unlikely that the T.R.U.E. Test can represent the more than 3,000 allergens currently reported in the literature. However, it will encompass the major allergens recognized by the NACDG and other contact dermatitis research groups.

It is important to note that the US regulatory path is challenging, especially for small foreign companies serving niche markets. For example, as of 2006, the T.R.U.E. Test must comply with the Pediatric Research Equity Act, which requires clinical trials of all panels (with the corresponding petrolatum allergens) in children. These

Table 1. Twelve New Allergens for T.R.U.E. Test Panel 3

<i>Substance</i>	<i>Status</i>	<i>Description</i>
Preservatives		
Diazolidinylurea (Germall II)	Release 2007	Formaldehyde-releasing preservative
Imidazolidinylurea (Germall 115)	Release 2007	Formaldehyde-releasing preservative
Bronopol	Clinical trials	Formaldehyde-releasing preservative
Methyldibromoglutaronitrile	Clinical trials	Preservative
Corticosteroids		
Tixocortol-21-pivalate	Release 2007	Corticosteroid class A
Budesonide	Release 2007	Corticosteroid class B
Hydrocortisone-17-butyrate	Clinical trials	Corticosteroid class D2
Other		
Bacitracin	Clinical trials	Antibiotic
Quinoline mix	Release 2007	Medicaments
Disperse Blue 106	Clinical trials	Textile dye
Gold sodium thiosulfate	Clinical trials	Metal
Parthenolide	Clinical trials	Feverfew extract (screen for sesquiterpene lactone allergy)

Adapted from Allerderm Clinical Research Department, Phoenix, AZ, and Mekos Laboratories, Hillerød, Denmark, personal communication, July 2007.

clinical trials will begin in the United States and Europe by late 2007.

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Successful Patch Testing despite Concomitant Low-Dose Prednisone Use

To the Editor:

While it is optimal to perform patch testing when patients are off prednisone to avoid suppressing positive reactions, at times patients require oral corticosteroids during patch testing. We describe a patient with an acute generalized eruption temporally associated with starting levothyroxine. Our patient required low-dose prednisone during patch testing because we were unable to clear her. Patch testing delineated causative cosmetic and textile allergens and was extremely beneficial despite concomitant prednisone use.

A 22-year-old woman presented with complaints of redness, pruritus, and soreness beginning on her face and chest and spreading to her trunk and lower extremities for 5 days.

Her history was significant for a left thyroidectomy performed 5 weeks prior to her eruption. Her medications included levothyroxine, which she had started 1 month prior to presentation. The patient was enrolled as a student and was feeling generally well.

On physical examination, she showed weeping papulovesicular plaques of the face, chest, back, abdomen, and upper and lower extremities. She was started empirically on dicloxacillin 250 mg four times daily for 7 days,

desonide ointment 0.05% for her facial dermatitis, and prednisone 30 mg daily in a tapering dose.

A Tzanck preparation and viral and bacterial cultures were negative. A 5 mm punch biopsy result was consistent with a hypersensitivity reaction, “possibly to drug.”

Given the fact that drug eruptions to levothyroxine are rare and this was a crucial medication for this patient, we were reluctant to stop her levothyroxine until allergic contact dermatitis (ACD) was ruled out. We were unable to clear her with the initial prednisone taper, and we therefore maintained her on 10 mg prednisone during patch testing.

She was tested to a modified North American Contact Dermatitis Group Standard, fragrance, cosmetic/preservative, textile, hair, and rubber series (Chemotechnique Diagnostics, Vellinge, Sweden) using Finn Chambers on Scanpor tape (Epitest Ltd OY, Tuusula, Finland). The patches were removed at 48 hours, and readings were performed at 48 and 72 hours.

At 72 hours, she showed ++ reactions to formaldehyde, hexahydro-1,3,5-tris-(2-hydroxyethyl) triazine (Grotan BK Vellinge, Sweden), and benzalkonium chloride. She showed + reactions to p-phenylenediamine, dimethylol dimethyl (DMDM) hydantoin, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI), dimethylol dihydroxyethyleneurea (Fixapret CPN, Chemotechnique Diagnostics), melamine formaldehyde, urea formaldehyde, and sorbitan sesquileate. She showed questionable reactions to the following: benzophenone-4, Disperse Yellow 3, Disperse Red 1, Disperse Blue 106, 4-aminophenol, hydroquinone, and diphenylguanidine.

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